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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/943,664 | 08/30/2001 | David Botstein | P2548P1C8 | 2448 |

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| EXAMINER | |
|---|---|
| O HARA, EILEEN B | |

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| 1646 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Advisory Action Before the Filing of an Appeal Brief | Application No. 09/943,664 | Applicant(s) BOTSTEIN ET AL. | |
|---|---|---|---|
| | Examiner Eileen B. O'Hara | Art Unit 1646 | |

*--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

THE REPLY FILED 11 May 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: 27-34.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

## ATTACHMENT TO ADVISORY ACTION

11. NOTE: The rejections are maintained. HOWEVER, upon further consideration, the examiner no longer asserts that mRNA levels are not predictive of polypeptide levels. Therefore, the following references are no longer being relied upon to support the rejections: Chen et al., Hu et al., Haynes et al., Gygi et al., Lian et al., Fessler et al., Greenbaum et al., Nagaraja et al., Waghray et al., Sagnaliev et al., Lilley et al., King et al., Bork et al., Madoz-Gurpide et al. The following references cited by Applicant pertaining to the mRNA/polypeptide correlation issue will no longer be addressed: Futcher et al., Alberts and Lewin, Zhigang et al., Meric et al., Wang et al., Munaut et al., Celis et al., Maruyama et al., Rudlowski et al., and the following declarations, Polakis I and II and Scott. The basis of the maintained rejections is solely that gene amplification levels (genomic DNA levels) are not predictive of mRNA or polypeptide levels. This issue has been thoroughly addressed on the record both by the examiner and Applicant.

Applicant's arguments pertaining to the remaining issue (after final response, 11 May 2007) have been fully considered but are not found to be persuasive for the following reasons.

Applicants argues that the PTO has recognized that Applicants' asserted utility is sufficient by issuing U.S. patent No. 7,208,308, with claims supported by the same utility as the utility asserted herein, e.g. claims 1, which states that the claimed polypeptide is encoded by a nucleic acid that is amplified in lung or colon tumors. Applicants assert that the protocols and procedures of the gene amplification experiment in the '308 patent (Example 92) and the present application (Example 28) are identical, and in addition, the ΔCt values resulting from these gene amplification experiments are similar.

Applicants' arguments have been fully considered but are not deemed persuasive. The actions of other Examiner's are not binding in the prosecution of an application by another Examiner.

Applicant relies on Ornoft et al., Hyman et al., and Pollack et al. as evidence that gene amplification increases mRNA expression in general. Specifically, regarding Ornoft et al., Hyman et al., and Pollack et al., these references have been extensively discussed on the record. The evidence has been considered anew, and the examiner maintains her positions regarding these pieces of evidence. The preponderance of the evidence supports maintaining the rejections.

Applicants disagree with the Examiner's interpretation that Godbout teaches that amplified genes are only overexpressed if they provide a selective advantage. Applicants argue that Godbout, which focuses on co-amplified genes, states that it is unlikely that a gene located about 400 kb from the MYCN gene will be consistently amplified as an intact unit unless its product provides a growth advantage to the cell (page 21162 of Godbout), and thus, rather than conclude that an amplified gene must encode a polypeptide that provides a selective advantage, Godbout suggests that the selective advantage plays a role in why a particular gene may be co-amplified with another gene. Applicants submit that this aspect of the Godbout teachings is not relevant to Applicants' assertion of utility, which is not based on any gene that is alleged to be co-amplified. Further, Applicants note that regardless of the co-amplification aspect of the Godbout reference, this reference teaches that a DEAD box gene, DDXl, shows good correlation between gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cancer cell lines studied. (See pages 21164, 21167, and 21168.)

The general concept of gene amplification's lack of correlation with mRNA/protein overexpression was addressed with reference to Sen in the Office Action mailed 24 March 2003. Specifically, cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr. Opin. Oncol. 12:82-88). The data presented in the specification were not corrected for aneuploidy. A slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Furthermore, Godbout et al. speak to general lack of correlation between gene amplification and mRNA/protein overexpression. The abstract of Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, **a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified.**" (emphasis added). The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state ***"It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell*** (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR)

are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." (emphasis added). There is no evidence that PRO347confers any growth advantage to a cell, and thus it cannot be presumed that the protein is overexpressed because the gene is amplified.

At page 9 of the response Applicants assert that Dr. Polakis' declarations are even more persuasive evidence demonstrating that for 62 differentially expressed gene transcripts a correlation was observed between gene amplification and protein overexpression. In addition, Applicants note that the Polakis Declarations were submitted and considered by the PTO in allowing the '308 patent.

Applicants' arguments have been fully considered but are not deemed persuasive. The Polakis Declarations addressed the correlation between mRNA levels and protein levels, and did not address any correlation between gene amplification and mRNA levels.

In view of the preponderance of evidence supporting the rejections (Pennica et al., Sen, Godbout et al., all of which are of record and have been previously discussed), the rejections are properly maintained.

Therefore, the preponderance of the totality of the evidence, considered anew, supports maintenance of the rejections.

It is believed that all pertinent rejections have been addressed.

Eileen B. O'Hara

EILEEN B. O'HARA
PRIMARY EXAMINER